Chiral Recognition of α-Amino Esters on the Chiral Helical Surface of Zinc Bilinone

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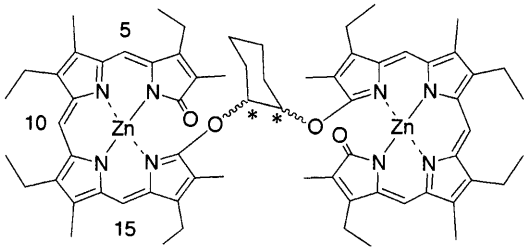
Chiral recognition of α-amino esters was examined using the homochiral helical dimer of the zinc complex of linear tetrapyrrole (zinc bilinone) as a host. ^{1}H NMR and thermodynamic studies indicated that favorable (Phe–OMe and Leu–OMe) or unfavorable (Asp–$(OMe)_2$) interactions of the side chain of α-amino esters with zinc bilinone lead to enantioselectivity.

Chiral recognition using artificial host molecules has contributed to model studies on naturally occurring molecular recognition events such as enzyme–substrate and receptor–signal molecule interactions[1,2] as well as development of analytical[3] and separating[4] devices for chiral molecules. Thus, a variety of chiral hosts have been prepared, and their chiral recognition properties have been extensively investigated. In general, chiral hosts are classified into two types; intrinsically and extrinsically chiral hosts.[2] Among them, the former, which possesses a chiral framework by itself, is expected to exhibit effective enantioselective binding of chiral guest molecules because it is possible to construct asymmetric space around the binding site. In this regard, a host molecule with a chiral helical framework is one of good candidates for intrinsically chiral hosts. Preparation of intrinsically chiral host requires, however, asymmetric synthesis and/or optical resolution. We avoid this problem by inducing helical chirality using intramolecular interaction with a simpler and easily accessible chirality. One-pot reaction of zinc oxaporphyrin with chiral cyclohexanediol yielded helical zinc bilinone (ZnBL) **1** whose helical chirality was completely regulated.[5,6] Thus readily accessible chirality of a chiral diol was converted to helical chirality, which is utilized as a chiral recognition motif. Here we show binding of amines and α-amino esters to **1** occurs enantioselectively, and favorable or unfavorable interactions of the side chain of α-amino esters with the helical framework of ZnBL lead to enantioselectivity.



PP-**1**; *trans*-(1*R*,2*R*)-cyclohexanedioxy
MM-**1**; *trans*-(1*S*,2*S*)-cyclohexanedioxy

We employed *PP*-**1** and *MM*-**1**, which have (1*R*,2*R*)- or (1*S*,2*S*)- cyclohexanediol as a spacer, respectively.[7] A ZnBL derivative forms a 1:1 complex with amine or α-amino ester, through the coordination of the amino group to the zinc.[8] In Figure 1 is shown a typical example of ^{1}H NMR spectral changes

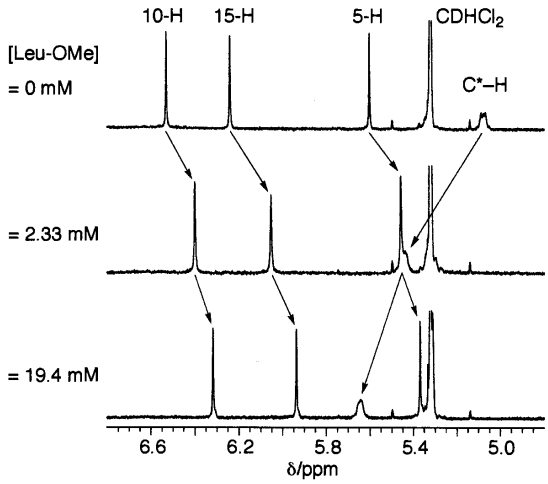


Figure 1. 500 MHz ^{1}H NMR spectra of *PP*-**1** in the presence of varying concentrations of D-Leu-OMe in CD_2Cl_2 at 223 K.

for complexation of *PP*-**1** with D-leucine methyl ester (D-Leu–OMe).[9] The signal of each proton shifted successively upon addition of amine or α-amino ester, showing a saturation behavior as shown in Figure 2. In the Job's plot for complexation of *MM*-**1** and (*R*)-NEA,[9] the maximum value was observed at [**1**]/([**1**] + [NEA]) = 0.5 when the total concentration of the host and the guest was 5.0×10^{-4} M, whereas it was observed at [**1**]/([**1**] + [NEA]) = 0.4 when the total concentration increased to 1.0×10^{-2} M. Therefore, host **1** forms a 1:2 complex with amines and α-amino esters via formation of the 1:1 complex under the present conditions. Assuming that each ZnBL unit operates independently as a recognition site for a guest molecule, the computer-assisted least squares analysis of the ^{1}H NMR chemical shift changes as a function of the concentration of the guest afforded satisfactory fitting of the experimental data to the calculated curve (Figure 2), determining averaged binding constants of each ZnBL unit for various guests as described in Table 1.

The ZnBL units in **1** adopt highly stable, chiral structure, and the helix inversion did not occur upon complexation with D- or L-isomer of the guest. The *P*-helical ZnBL skeleton exhibited higher affinity to D-amino esters employed here than the L-iso-

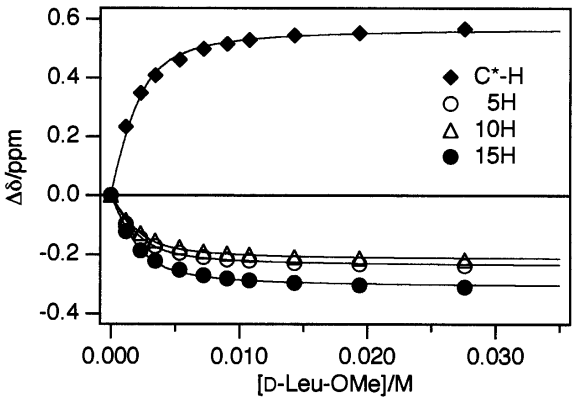


Figure 2. ^{1}H NMR chemical shift changes of the selected protons in *PP*-**1** upon complexation with D-Leu-OMe. The conditions are the same as described in Figure 1. The solid curves are the theoretical ones obtained by least-squares analysis, assuming the 1:1 complexation between each ZnBL unit and Leu-OMe.

Table 1. Apparent binding constants K for complexation of a ZnBL unit in *PP*-**1** with various α-amino esters and amines in CD_2Cl_2 at 223 K

guest	K /M^{-1} (s.d.)	$\Delta G°$ /kcal mol^{-1}	$\Delta\Delta G°$ /kcal mol^{-1}
Gly-O^{t}Bu	1070 (30)	–3.09	——
D-Asp-$(OMe)_2$	1030 (20)	–3.07	–0.54
L-Asp-$(OMe)_2$	303 (9)	–2.53	
D-Phe-OMe	1680 (50)	–3.29	–0.43
L-Phe-OMe	642 (26)	–2.86	
D-Leu-OMe	1490 (90)	–3.24	–0.34
L-Leu-OMe	699 (25)	–2.90	
D-Ala-OMe	924 (95)	–3.03	–0.32
L-Ala-OMe	458 (10)	–2.71	
(*S*)-NEA	3500 (290)	–3.62	–0.39
(*R*)-NEA	1470 (40)	–3.23	

mers. The comparison of free energy changes on complexation $\Delta G°$ between the set of enantiomers afforded an index of enantioselectivity $-\Delta\Delta G°$, of which trend is Asp–$(OMe)_2$ [9] > Phe–OMe [9] > Leu–OMe ≈ Ala–OMe.[9] Regarding the $\Delta G°$ for Gly–O^{t}Bu as a reference free energy change of coordination by an amino group, the enatioselectivity for Asp–$(OMe)_2$ originates mainly from the less stability of *PP*-**1**·L-Asp–$(OMe)_2$ than that of *PP*-**1**·D-Asp–$(OMe)_2$, whereas, in the cases of Phe–OMe and Leu–OMe, both of the stabilization of *PP*-**1**·D-isomer and the destabilization of *PP*-**1**·L-isomer contribute to the enantioselectivity. Especially, the relatively large values of the K for D-Phe–OMe and D-Leu–OMe indicate that the side chains of the D-isomers interact favorably with the bilinone skeleton through aromatic stacking and van der Waals interaction, respectively. Indeed, as shown in Figure 3, the signal of the 15-H in *PP*-**1** shifted remarkably upfield upon complexation with D-Phe–OMe, indicating the phenyl group in the side chain is located on the C-ring. Thus there is not a free rotation along the Zn–N (guest) bond, and a preferred orientation of the guest leads to the

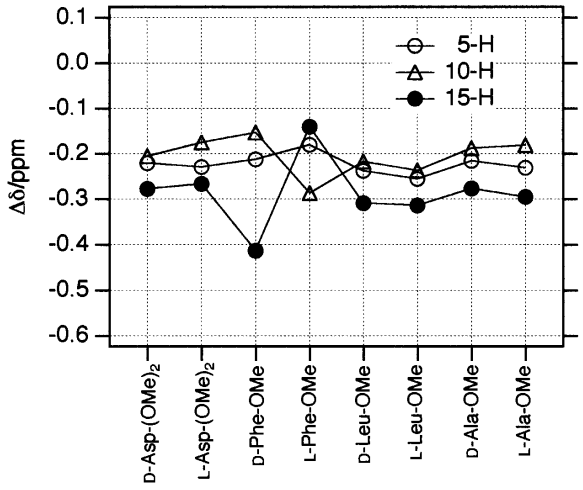


Figure 3. ^{1}H NMR chemical shift changes of the selected protons in *PP*-**1** upon complexation with α–amino esters in CD_2Cl_2 at 223 K.

chiral recognition. It is quite interesting that the enantioselective binding is achieved without any directional interactions such as hydrogen bonding except the coordination of the amino group to the zinc ion.

In summary, we demonstrated chiral recognition of α-amino esters and amines by the helicity-regulated zinc bilinone dimer **1**. To the best of our knowledge, this is the first example of chiral recognition on a chiral helical surface of a metal complex, which describes possibility for simple molecules with intrinsic chirality to operate as chiral hosts. Furthermore, such a chiral helical metal complex can serve as a chiral coordination compound catalyst for asymmetric synthesis. Further research is now under investigation.

References and Notes

1 T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev.*, **22**, 383 (1993); Y. Kubo, *Synlett*, **1999**, 161.
2 H. Ogoshi and T. Mizutani, *Acc. Chem. Res.*, **31**, 81 (1998); H. Ogoshi, T. Ema, Y. Kato, T. Mizutani, and Y. Kuroda, *Supramol. Chem.*, **6**, 115 (1995).
3 B. Chankvetadze, G. Endresz, and G. Blaschke, *Chem. Soc. Rev.*, **25**, 142 (1996); Y. Kubo, S. Maeda, S. Tokita, and M. Kubo, *Nature*, **382**, 522 (1996); T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Nature*, **374**, 345 (1995).
4 Y. Okamoto and E. Yashima, *Angew. Chem., Int. Ed. Engl.*, **37**, 1020 (1998); W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.*, **89**, 347 (1989).
5 S. Yagi, N. Sakai, R. Yamada, H. Takahashi, T. Mizutani, T. Takagishi, S. Kitagawa, and H. Ogoshi, *Chem. Commun.*, **1999**, 911.
6 For reviews of helical metal complexes, see: U. Knof and A. von Zelewsky, *Angew. Chem., Int. Ed. Engl.*, **38**, 303 (1999); C. Piguet, G. Bernardinelli, and G. Hopfgartner, *Chem. Rev.*, **97**, 2005 (1997).
7 *P*- and *M*-Helicity refer to right-handed and left-handed screw-sense helicity, respectively.
8 T. Mizutani, S. Yagi, A. Honmaru, S. Murakami, M. Furusyo, T. Takagishi, and H. Ogoshi, *J. Org. Chem.*, **63**, 8769 (1998); T. Mizutani, S. Yagi, A. Honmaru, and H. Ogoshi, *J. Am. Chem. Soc.*, **118**, 5318 (1996).
9 Abbreviation: Asp–$(OMe)_2$, aspartic acid dimethyl ester; Phe–OMe, phenylalanine methyl ester; Ala–OMe, alanine methyl ester; NEA, 1-(1-naphthyl)ethylamine.